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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/828,592	04/06/2001	Timothy Walston	13735.1USU1	5683

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EXAMINER
MONDESI, ROBERT B

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/12/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/828,592	WALSTON ET AL.	
	Examin r	Art Unit	
	Robert B Mondesi	1653	

-- Th MAILING DATE of this communication appears on the cover sheet with th corr spond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *25-48* is/are pending in the application.

4a) Of the above claim(s) *35-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *25-34* is/are rejected.

7)☐ Claim(s) *29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04-06-01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 25-34 , drawn to modified amino acid sequences, classified in Class 530, subclass 393.

II. Claims 35-44, drawn to nucleic acid sequences, classified in Class 536, subclass 23.5 .

III. Claims 45-48, drawn to methods of utilization of modified antithrombin , classified in class 530, subclass 381.

The inventions are distinct, each from the other for the following reasons:

1. Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are capable of separate use and function. While the polynucleotides may encode the protein, the polynucleotide can not be substituted for the polypeptide. In the alternative the polypeptide is not substitutable by the polynucleotide. For example, a polypeptide cannot be used in a transcription assay.

2. Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant the product as is being claimed can be used in materially different process such as production of monoclonal Anti-bodies.

3. The inventions of Groups II and III are unrelated in that the product of group II is not the product used in the process of group III.

Because these inventions are distinct for the reasons given above and since they have acquired a separate status in the art as shown by their different classification and/or divergent subject matter, and/or are separately and independently searched, restriction for examination purposes as indicated is proper.

822 Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 C.F.R. 1.143).

4. During a telephone conversation with Ms Nancy Parsons on 07-15-03 a provisional election was made to traverse to prosecute the invention of Group I drawn to a composition (claims 25-34). Affirmation of this election must be made by applicant in replying to this Office action. Claims 35-48 withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

BM 7-15-03

Preliminary Amendment

The preliminary amendment filed 7/10/2003 has been entered. Claims 1-24 have been canceled; and new claims 25-48 added. The pending claims are 25-48

Information Disclosure Statement

The IDS filed 04/06/2002 has been received, entered and considered. A signed copy is attached.

Claim Objections

6. Claim 28 is objected to because of the following informalities: The word, "the", at the end of the first line is redundant. Appropriate correction is required.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 25-34 are rejected under 35 U.S.C. 101 because the claimed invention is directed to nonstatutory subject matter. Given the existence of naturally occurring mutation(s), (Hematology, (October, 2002) vol. 36. No. 4 Part 2, pp. 370A and Journal of Biological Chemistry, (November 8 2002) Vol. 277, No. 45, pp. 43058-43063), the phrase modified anti-thrombin does not assert the presence of "hand of man". The polypeptide as claimed, has an amino acid sequence duplicative of that of the protein in Thrombosis Research, (1994) Vol. 76, No. 3, pp.307-315 or the cellular precursor

thereof and possesses the biological and functional properties of the naturally occurring polypeptide Anti-thrombin and therefore does not constitute patentable subject matter absent isolated and purified.

See *American Wood v. Fiber Disintegrating Co.*, 90 U. S. 566 (1974); *American Fruit Growers v. Brogdex Co.*, 283 U. S. 1 (1931); *Funk Brothers Seed Co. v. Kalo Inoculant*, 33 U. S. 127 (1948); and *Diamond v. Chakrabarty*, 206 USPQ 193 (1980).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 25-29 and 31-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claims 25-28, a variety of modified Anti-thrombin proteins are being claimed, each of which having an unlimited number of substitutions in the H-Helix region, wherein negatively charged amino acids have been substituted with positively charged or neutral amino acids. However, the specification shows evidence of only four Anti-thrombin mutants, where negatively charged amino acids in the H-Helix, have been substituted with positively charged or neutral amino acids. (Table 3, Page 14.) The applicant has

only shown or described the method of making four modified Anti-thrombin mutants. It would not have been apparent to a person of skill in the art to have expected different mutations to have resulted in Anti-thrombin mutants that have the identical chemical, physical and biological features and function of the disclosed unmodified or mutated Anti-thrombins of the examples.

Emmerich, J. (Thrombosis Research, 1994 Vol. 76, No. 3, pp. 305-315) shows that in order to accurately analyze the phenotypic consequences of a mutation, a working example of the supposed entity must be present. The genomic analysis of this study revealed a substitution of Phe 402 by Leu. This mutation involves an amino acid located in the carboxyterminal side of anti-thrombin reactive loop, the expression of the mutation is pleiotropic and results in a reduction in the circulating concentration of Anti-thrombin and impairs both its Anti-thrombin activity and its ability to bind heparin. Emmerich, further shows that the Phe to Leu mutation at position 402 decreased the sensitivity of Anti-thrombin to denaturation, suggesting that the mutation increases the stability of the protein. By duplicating the steps in the materials and methods of the said reference, it is possible for a person of skill in the art to obtain the said product. Without the presence of a working example of this product, it would not have been possible for Emmerich to show the importance of this pleiotropic mutation in regards to the function and activity of Anti-thrombin. The same is also true in the case of other anti-thrombin mutants. It would not be possible for a person of skill in the art to know the specific characteristic and function of a given modified Anti-thrombin mutant without the ability to produce it.

In claim 29, none of the AT-mutants or SEQ ID #s in the specifications represent or show a peptide containing substituted arginine (Arg,R) in positions 309, 310, 312 or 313 as is claimed.

Claims 31-34 are dependent claims and depend on claims 25 and 29 in order to define the modified anti-thrombin that is being claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 25,28,31-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More positive charge is a relative term, residues can be substitute to cause an overall change form net negative charge to neutral. Alternatively residues can be substituted to change the overall charge from neutral to positive. It is ambiguous whether the claim is referring to a net charge change from neutral to positive or a net charge change from negative to neutral.

It also must be noted that it possible to alter the net charge of a peptide by altering the side chains of specific amino acids. It is possible to modify the side chain of arginine for an increase in the net charge of Anti-thrombin, such modification will render the need to alter amino acid residues unnecessary, therefore demonstrating that modifications to cause an overall change in the net charge of a given poly-peptide can be performed by more than one method. This raises the question as to which method of modification is being stated in claims 25 and 28, hence making the claims indefinite.

Claims 31-34 are dependent claims that maintain the ambiguity of what is being claimed by not further limiting the independent claims.

Claims 31 and 32 refer to a pharmaceutical composition, a pharmaceutical composition by definition has more than one component, lack of a second component renders the claims indefinite.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 25-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over, Henry Jakubowski, (Journal of Biological Chemistry, Vol 262. No 8. pp 3876-3882), and Rebecca Shirk, (Journal of Biological Chemistry, Vol 269. No 46. pp 28690-28695).

Jakubowski, (Pages 3876-3879) teaches that the inhibitory effects of Anti-thrombin on Thrombin is reduced because of conformational changes that occur after the formation of Thrombin-thrombomodulin complex. Jakobowski, also teaches that this conformational change allows for preferential binding of protein C and protein C inhibitors (PCI) to Thrombin. What Jakubowski does not teach, is the molecular alteration that is required to increase the affinity of Anti-thrombin for Thrombin after the formation of Thrombin-thrombomodulin complex.

Shirk teaches that, basic and positively charged amino acids in H-Helix of PCI play a prominent role in the Heparin dependent acceleration of PCI inhibitory effect of the Thrombin–thrombomodulin and APC complexes **(claims 25-28).** On pages 28692 and 28693, Shirk shows that substitution of basic amino acids with neutral and negative amino acids in the H-Helix of PCI will lead to a decrease in the interaction of PCI and Heparin **(claims 25-28),** and in result causing a decrease in the inhibitory effect of Thrombin-thrombomodulin and APC complexes by PCI.

As combined, one of ordinary skill in the art would have had the claimed invention because Jakubowski teaches that the reason for the decreased inhibitory activity of Thrombin by Anti-thrombin is due to a conformational change that takes place after Thrombin is bound to Thrombomoldulin. This conformational change provides for the preferred binding of protein C and PCI molecules to the Thrombin . When Jakubowski is combined with Shirk, the result is an Anti-thrombin molecule that has an increased inhibitory activity towards Thrombin-thrombomoudulin complex. This increase in inhibitory activity is due to the fact that the H-helix of Anti-thrombin has been modified

to resemble that of PCI **(claims 25-28)**. As combined, the references demonstrate that one of ordinary skill in the art would have made and used the claimed invention prior to the time the claimed invention was made. Thus the claimed invention was prima facie-obvious at the time it was made.

Conclusion

12. None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert B Mondesi whose telephone number is 703-305-4445. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 703-308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

RBM
August 11, 2003

CHRISTOPHER S. F. LOW
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